CLAIMS

We claim:

1. A process for preparing leflunomide comprising the steps of
   a) chlorinating 5-methylisoxazole-4-carboxylic acid by contacting it with a chlorinating agent thereby forming crude 5-methylisoxazole-4-carboxylic acid chloride,
   b) optionally evaporating excess chlorinating agent or volatile byproducts of the chlorination under reduced pressure, whereby evaporation leaves a residue of unevaporated material containing 5-methylisoxazole-4-carboxylic acid chloride,
   c) contacting the so-formed crude 5-methylisoxazole-4-carboxylic acid chloride or residue with 4-trifluoromethylaniline in the presence of an alkali metal or alkaline-earth metal bicarbonate in an acylation solvent system comprising at least one solvent component selected from the group consisting of water, ethyl acetate, toluene and dimethyl acetamide, and
   d) isolating the leflunomide.
2. The process of claim 1 wherein the chlorinating step is conducted in the absence of N,N-dimethylformamide.
3. The process of claim 1 wherein the chlorinating step is conducted in the absence of a catalyst.
4. The process of claim 1 wherein the chlorinating step is conducted neat at a temperature of from about 40° to about 55°C.
5. The process of claim 1 wherein 5-methylisoxazole-4-carboxylic acid is contacted with the chlorinating agent in an inert chlorination solvent at a temperature of from about 50°C to about 80°C.
6. The process of claim 5 wherein the inert chlorination solvent is toluene.
7. The process of claim 1 wherein the chlorinating agent is selected from the group consisting of thionyl chloride, oxalyl chloride, benzoyl chloride, PCl_5 and PCl_3.
8. The process of claim 7 wherein the chlorinating agent is thionyl chloride.
9. The process of claim 1 wherein the at least one solvent component of the acylation solvent system is water.

10. The process of claim 1 wherein the acylation solvent system is a mixture of toluene and water.

11. The process of claim 1 wherein the acylation solvent system is a mixture of toluene and N,N-dimethyl acetamide.

12. The process of claim 1 wherein the crude 5-methylisoxazole-4-carboxylic acid chloride or residue is contacted with 4-trifluoromethylaniline at a temperature of from about 20°C to about 65°C.

13. The process of claim 12 wherein the crude 5-methylisoxazole-4-carboxylic acid chloride or residue is contacted with 4-trifluoromethylaniline at a temperature of from about 40°C to about 60°C.

14. The process of claim 1 wherein the crude 5-methylisoxazole-4-carboxylic acid chloride or residue is contacted with from about 1 to about 1.2 molar equivalents of 4-trifluoromethylaniline with respect to 5-methylisoxazole-4-carboxylic acid.

15. The process of claim 1 wherein the alkali metal or alkaline-earth metal bicarbonate is present in from about 1.05 to about 1.2 molar equivalents with respect to the 5-methylisoxazole-4-carboxylic acid chloride.

16. The process of claim 1 wherein contacting the crude 5-methylisoxazole-4-carboxylic acid chloride or residue with 4-trifluoromethylaniline is conducted at a concentration of from about 4 to about 14 volumes of the acylation solvent system per one weight part of 5-methylisoxazole-4-carboxylic acid chloride.

17. The process of claim 16 wherein contacting the crude 5-methylisoxazole-4-carboxylic acid chloride or residue with 4-trifluoromethylaniline is conducted at a concentration of from about 4 to about 14 volumes of the acylation solvent system per one weight part of 5-methylisoxazole-4-carboxylic acid chloride.

18. The process of claim 1 wherein the leflunomide is isolated by precipitation from the acylation solvent system.

19. The process of claim 18 wherein the leflunomide is precipitated at a temperature of from about 0°C to about 25°C.

20. The process of claim 18 wherein the leflunomide obtained by precipitation is substantially free of N-(4-trifluoromethylphenyl)-2-cyano-3-hydroxycrotonamide.

21. The process of claim 20 wherein the leflunomide obtained by precipitation contains about 150 ppm or less of N-(4-trifluoromethylphenyl)-2-cyano-3-hydroxycrotonamide.

22. The process of claim 21 wherein the leflunomide obtained by precipitation contains about 100 ppm or less of N-(4-trifluoromethylphenyl)-2-cyano-3-hydroxycrotonamide.

23. The process of claim 22 wherein the leflunomide obtained by precipitation contains about 50 ppm or less of N-(4-trifluoromethylphenyl)-2-cyano-3-hydroxycrotonamide.

24. The process of claim 23 wherein the leflunomide obtained by precipitation contains about 10 ppm or less of N-(4-trifluoromethylphenyl)-2-cyano-3-hydroxycrotonamide.

25. The process of claim 18 wherein the leflunomide obtained by precipitation is substantially free of 5-methyl-N-(4-methylphenyl)-isoxazole-4-carboxamide.

26. The process of claim 18 wherein the leflunomide obtained by precipitation is substantially free of N-(4-trifluoromethylphenyl)-3-methyl-isoxazole-4-carboxamide.

27. Leflunomide prepared by a process comprising the steps of:

a) providing 5-methylisoxazole-4-carboxylic acid chloride and

b) contacting the 5-methylisoxazole-4-carboxylic acid chloride with 4-trifluoromethylaniline in the presence of an alkali metal or alkaline-earth metal bicarbonate in an acylation solvent system comprising at least one solvent component selected from the group consisting of water, ethyl acetate, toluene and dimethyl acetamide, and

c) isolating the leflunomide.

28. The leflunomide of claim 27 wherein 5-methylisoxazole-4-carboxylic acid chloride is provided as crude 5-methylisoxazole-4-carboxylic acid or a residue by:

a) chlorinating 5-methylisoxazole-4-carboxylic acid by contacting it with a chlorinating agent to form crude 5-methylisoxazole-4-carboxylic acid chloride and

b) optionally evaporating excess chlorinating agent or volatile byproducts of the chlorination under reduced pressure, whereby the evaporation leaves a residue of unevaporated material containing 5-methylisoxazole-4-carboxylic acid chloride.

29. The leflunomide of claim 27 which is substantially free of N-(4-trifluoromethylphenyl)-2-cyano-3-hydroxycrotonamide.

30. The leflunomide of claim 29 containing about 150 ppm or less of N-(4-trifluoromethylphenyl)-2-cyano-3-hydroxycrotonamide.

31. The leflunomide of claim 30 containing about 100 ppm or less of N-(4-trifluoromethylphenyl)-2-cyano-3-hydroxycrotonamide.

32. The leflunomide of claim 31 containing about 50 ppm or less of N-(4-trifluoromethylphenyl)-2-cyano-3-hydroxycrotonamide.

33. The leflunomide of claim 32 containing about 10 ppm or less of N-(4-trifluoromethylphenyl)-2-cyano-3-hydroxycrotonamide.

34. The leflunomide of claim 27 which is substantially free of 5-methyl-N-(4-methylphenyl)-isoxazole-4-carboxamide.

35. The leflunomide of claim 27 which is substantially free of N-(4-trifluoromethylphenyl)-3-methyl-isoxazole-4-carboxamide.

36. The leflunomide of claim 27 substantially free of N-(4-trifluoromethylphenyl)-2-cyano-3-hydroxycrotonamide, 5-methyl-N-(4-methylphenyl)-isoxazole-4-carboxamide and N-(4-trifluoromethylphenyl)-3-methyl-isoxazole-4-carboxamide.

37. A pharmaceutical composition comprising the leflunomide of any of claims 27 through 36.

38. A pharmaceutical dosage form comprising the pharmaceutical composition of claim 37.

39. A method of treating rheumatoid arthritis comprising administering to a patient in need of such treatment a therapeutically effective amount of the leflunomide of any of claims 27 through 36.

40. A method of regulating cell proliferation comprising administering to a patient a an amount of the leflunomide of any of claims 27 through 36 sufficient to inhibit cell proliferation.